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Title: Subcutaneous injection of Tranexamic acid to reduce bleeding during dermatologic surgery: double blind, placebo controlled, randomized clinical trial

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Abstract

BACKGROUND Topical application, oral and IV injection of Tranexamic acid (TXA) have been used to reduce surgical bleeding.

OBJECTIVE To evaluate the safety and efficacy of TXA injected subcutaneously to reduce bleeding during dermatologic surgery.

METHODS In this double-blinded, placebo controlled, randomized prospective study, 131 patients were randomized to subcutaneous injection of lidocaine 2% diluted 1:1 with either saline (placebo) or TXA 100mg/1ml prior to surgery. Before the second stage or closure, size measurements of bloodstain impregnation on Telfa and surgical wound size were recorded and analyzed using mixed-effects linear regression. Subjective evaluation of hemostasis was performed using 4-point scale grading and analyzed using Fischer's exact test.

RESULTS 127 patients completed the study. The bloodstain to surgical wound size ratio was smaller in the TXA group (1.77) compared to the placebo group (2.49) ($p<0.001$). An improved effect of TXA on bleeding was observed in the subgroup of patients receiving anticoagulants (MD; 95% CI; -0.83; -1.20 to -0.46 $p<0.001$). The subjective hemostasis assessment was significantly better in the TXA group overall ($p=0.043$) and anticoagulant subgroup ($p=0.001$) compared to the placebo group.

CONCLUSION Subcutaneous injection of TXA was safe, reduced bleeding during dermatologic surgery and particularly effective for patients receiving anticoagulation treatment.

Key words: Tranexamic acid; hemostasis; anticoagulants; Mohs micrographic surgery

Introduction

Bleeding during dermatologic surgery is an inevitable part of the procedure. Its intensity is dictated by various factors such as surgery location, size and depth of the surgical wound, involvement of larger blood vessels, presence of high blood pressure and the use of medications that inhibit clotting. Dermatologic surgical procedures such as Mohs Micrographic Surgery (MMS) are usually safe and are not characterized by excessive blood loss; nevertheless, even a small amount of bleeding may obscure the surgical field and result in hematomas in the post-operative period. Attempts to minimize surgical bleeding include better control of blood pressure, local injection of adrenaline with anesthetic agent, using an electrocoagulation device during surgery and discontinuing anticoagulants prior to surgery. Excessive electrocoagulation contributes to tissue damage and may result in delayed wound healing, a higher tendency for infection, and a less than optimal scar.[1, 2] Discontinuing the use of anticoagulants before surgery is dangerous and may result in thromboembolic events such as stroke.[3, 4]

Anti-fibrinolytic drugs promote blood clotting by preventing the blood clot from breaking down. One of the commonly used anti-fibrinolytic drugs is tranexamic acid (trans-4-aminomethyl cyclohexane carboxylic acid) (TXA, Cyklokapron), a synthetic lysine analogue that reversibly blocks the binding sites of plasminogen and prevents plasminogen activation to plasmin and the lysis of polymerized fibrin in the blood clot.[5] TXA is low cost, readily available in a surgical setting and has been used routinely for many years to reduce bleeding both during and after surgery, and can be administered using IV, orally or topically. If there are no contraindications, TXA can be safely administered postoperatively to reduce healing time and minimise complications of bleeding such as bruising. It is used topically during tooth extraction, orthopedic procedures, cardiac surgery, and other surgical procedures.[6-9]

TXA is also used intravenously to reduce the need for blood transfusion in orthopedic,[10] cardiac,[11] and liver transplantation,[12] for children undergoing tonsillectomy [13] and to reduce the risk of re-bleeding within 24 hours after a subarachnoid hemorrhage.[14] TXA is also used to reduce blood loss after vaginal delivery and caesarian section when given as prophylaxis.[15]

TXA dosage varies widely, according to the literature and in clinical practice. TXA has a half-life elimination of 2-11 hours with 95% of the drug eliminated unchanged through the urine. The safety of TXA has been demonstrated in numerous publications. A systematic review that included 20,451 patients concluded that TXA reduces mortality in trauma patients with bleeding, without increasing the risk of adverse reactions such as vascular occlusive events (myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism).[16, 17] A single report suggests that high-dose TXA (≥100 mg/kg) is independently associated with an increased risk of early seizure in open heart surgery.[18] There is one case report of accidental intrathecal administration of a large dose of TXA resulting in convulsions and refractory ventricular fibrillation [19] and a case report of polymyoclonus seizure resulting from accidental intrathecal injection of TXA in spinal anesthesia.[20]

In this study we investigated the safety of the hemostatic-anesthetic mixture (containing TXA) injected subcutaneously and the efficacy of TXA in reducing bleeding. In order to assess the amount of bleeding from the wound we used a normalized measure of bloodstain size to surgical wound size ratio (Figure 1) as has been reported in our previous paper.[21] The effect of TXA on clot stabilization and reduction of bleeding in surgery and trauma, is well documented in the medical literature but is only described in oral consumption, topical application and IV injection. To the best of our knowledge, subcutaneous or intradermal injection of TXA for the purpose of intra and post-operative bleeding reduction has not

previously been reported.

Materials and Methods

This is a single-center, double-blind, prospective, randomized, clinical study. The protocol was approved by the local ethics committee at the Sheba Medical Center (approval number SMC-1079-14). The study was conducted in accordance with the declaration of Helsinki, and written informed consent was obtained from all participants prior to their undergoing surgery. All patients who were referred to Mohs Micrographic surgery (MMS) for head and neck skin cancer were offered to participate in this study. Exclusion criteria were: systolic blood pressure greater than 200 mmHg, surgical wound size greater than 4 cm, unwillingness of patient to sign the informed consent, a known allergy to TXA, a known history of personal or familial coagulation disorder. Patients receiving anticoagulants were not excluded and note of the drug type and whether or not it was discontinued prior to surgery was recorded. Patient stopping acetylsalicylic acid for less than 5 days were considered as still taking acetylsalicylic acid. Prior to surgery the following data was collected: demographic data, concurrent medical conditions, smoking status and systemic medications (specifically, anticoagulation treatment and when the last dose had been taken).

One hundred and fifty patients were assessed for eligibility with the aim to enroll a minimum of 100 participants. Nineteen patients did not meet the inclusion/exclusion criteria. One hundred and thirty-one patients that participated in the study were randomized into either the TXA group or the placebo group (Table I). All the surgical procedures and measurements were performed by a single surgeon. All the dressings were done by the same nurse. The patient blood pressure was recorded before each MMS stage and the pulse was monitored continuously with a pulse oximeter. MMS was performed under local anesthesia. After

marking the skin, the surgeon injected each patient subcutaneously with a mixture of 2% lidocaine with either TXA 100 mg/1 ml (TXA group) or normal saline 0.9% sodium chloride (placebo group) in a 1:1 mixture. This created a final mixture with an effective 1% lidocaine as an anesthetic agent in both groups and a TXA concentration of 50 mg/ml in the TXA group. The TXA solution was mixed with lidocaine in the same syringe. We have presented in our previous study that the mixture (TXA + Lidocaine) does not interfere with the anti-fibrinolytic action of TXA. [21] Adrenaline was not added to the anesthetic solution during the study phase.

The different mixtures were prepared in coded identical 1cc insulin syringes by the study nurse prior to surgery. There were equal number of syringes in the two groups. The surgeon randomly chose the syringe for each case. The coding list was opened only after the completion of the study. The surgeon and patient were unaware of the type of mixture that was used. The mixture was injected subcutaneously until the patient reported no pain when checking with a needle prick. The total amount injected varied according to the tumor size and patient individual pain tolerance. Average volume injected was between 1-6 cc. To allow a significant effect of the mixture the surgeon waited 15 min before starting the surgery. After the first MMS stage, a routine hemostasis was performed with a standard electrocautery device (Bovie) with a Collorado tip, set up to level 20 kHz strength and used directly on points of bleeding or through fine jeweler's forceps where small arterioles were nicked. The electrocoagulation was performed using short pulses until bleeding was fully controlled. The surgical wound was covered with a 6x6 Telfa AMD® pad attached to the wound and one folded 10x10 gauze on top of that, secured with a Micropore tape.. The patient was then transferred to the waiting area until the second MMS stage or reconstruction procedure. After 30 minutes, the patient was returned to the surgical unit and the dressing was removed. At

this stage, two measurements were taken and recorded; the long axis of the surgical wound and the long axis of the blood stain impregnation on the Telfa pad (Figure 1). This model for measuring a small amount of bleeding is more accurate than gauze weighing, because of the difference in order of magnitude between the weight of the blood soaked in the gauze and the gauze weight itself.

Subjective evaluation of hemostasis was performed by a single surgeon using a 4-point ordinal scale as: *Excellent*: Better than expected/predicted in this type of procedure; *Good*: As expected in this type of procedure with minimal oozing; *Moderate*: Less than optimal for the type of procedure with moderate oozing but no need to add gauze dressing and; *Poor*: pinpointed oozing without a presence of a pumping vessel, that needed adding gauze dressing and some local pressure [22]. The same surgeon also recorded whether he believed the solution contained TXA or not, based on his subjective assessment of whether he saw a blood clot in the surgical wound and on the 4-point scale. From this stage on, the surgery resumed routinely as is customary in our practice, at the second stage of the Mohs surgery or repair: bupivacaine (5mg/ml) with adrenaline (final concentration of (1:200,000) was injected to both study arms (1-3cc).

Analyses were performed on the transformed (inverse) data because the raw data for blood stain to surgical wound size ratio was not-normally distributed. The comparative results are shown as mean difference with 95% confidence intervals but p values are from the transformed variable. Graphs were plotted using Prism 7 (GraphPad Software Inc., California, USA). Ratio for bloodstain size to wound size for placebo and TXA groups were compared using mixed effect linear regression (Stata, v. 14, StataCorp, TX, USA). All data were analyzed with and without adjusting for any effect of confounders including age and

sex. Data for surgeon's assessments of hemostasis and type of intervention were analyzed using Fischer's Exact test. Subgroup analyses were performed between the two interventions to compare participants taking anticoagulants and those not taking anticoagulants.

Results

Data was collected between November 10th, 2014 and December 19th, 2016. One hundred and thirty-one patients took part in the study (67 in the placebo and 64 in the TXA group). Four patients were excluded from data analysis (Figure 2). In three cases, a small pumping arteriole was detected at the time of dressing removal which obscured proper measurement of perfused bleeding. In one patient, an allergic reaction was suspected due to redness and local edema that was noticed 5 minutes after the injection. The patient was excluded from the study and reported by the study nurse to be injected with TXA. The local signs disappeared spontaneously after 2 hours without further sequelae.

Baseline characteristics of the study participants are presented in Table 1. The surgical wound size for the TXA group was significantly larger than the placebo group. There was no difference in the bloodstain size between the two groups. The ratio of bloodstain to surgical wound size was smaller in the TXA group compared to the placebo group (MD; 95% CI; -0.72; -1.09, -0.35; $p<0.001$) (Table 2). These comparative results did not change after controlling for the potential confounders of age and sex.

A greater effect of TXA on the blood stain to surgical wound size ratio was observed in the anticoagulant subgroup. Patients on anticoagulants in the TXA group had significantly lower bloodstain size to surgical wound size ratio than those in the placebo group (MD; 95% CI; -0.83; -1.20 to -0.46 $p<0.001$). Similarly, patients not on anticoagulants (anticoagulant free) in

the TXA group had significantly lower bloodstain size to surgical wound size ratio than those in the placebo group (MD; 95% CI; -0.60; -1.18 to -0.01 p=0.045) (Figure 3)

The haemostasis assessment performed by the surgeon (including all patients) using the 4-point scale was significantly better (p=0.043), with larger number of *Excellent* and *Good* assessments in the TXA group compared to the placebo group (Figure 4). Furthermore, in the anticoagulant subgroup the haemostasis evaluation was significantly better (p=0.001), with larger number of *Excellent* and *Good* assessments for the TXA group (92.8%) compared to the placebo group (57.2%). However, no significant differences were observed for the anticoagulant-free subgroup (Table 3). The surgeon's assessment of whether the patient was on TXA or placebo was correct more often (p=0.001) for the TXA group (63.3%) than for the placebo group (32.8%). Furthermore, the subgroup analysis showed the surgeon's assessment of TXA/placebo was correct more often for the TXA group than for the placebo group in both the anticoagulant (p=0.008) and non-anticoagulant (p=0.038) subgroups.

Discussion

In this study, TXA solution injected subcutaneously together with lidocaine before MMS, demonstrated a significant hemostatic effect compared to lidocaine with saline. The decrease in bloodstain to defect ratio and significantly improved haemostasis assessment for subcutaneous TXA injection is due reversibly blocking plasminogen binding sites preventing activation to plasmin and lysis of polymerized fibrin in clotting. These results were more pronounced in patients taking anticoagulation drugs such as acetylsalicylic acid (Aspirin), coumadin (Warfarin), eliquis (Apixaban), clopidogrel (Plavix), enoxaparin (Clexane) and rivaroxaban (Xarelto). The explanation for this phenomenon may be shifting of the equation, bleeding to clot formation, to the right regardless the anticoagulant that was taken (Figure 5).

While blood clotting is a normal phenomenon in patients that are not taking anticoagulants, the effect of anti-fibrinolytic agents are more pronounced in patients on anticoagulants with impaired clotting cascades.

Subcutaneous injection of lidocaine with TXA was well tolerated in our study with only one reported adverse outcome, a mild local allergic reaction that quickly resolved. No thromboembolic events were noted. Previous studies have suggested not to discontinue anticoagulation treatment during dermatologic surgery despite an increase in bleeding in order to minimize the possible risk of serious thromboembolic complications.[23] This work presents a method to minimize the increased bleeding in patients under anti coagulation treatment by locally propagating coagulation effect.

Dermatologic surgeons are trying constantly to reduce pain during local anesthesia, using different injection techniques [24] and routinely buffering the anesthetic solutions with bicarbonate.[25, 26] Hence, an additional benefit of TXA may be its buffering effect. With a pH of between 6.5 to 8,[27, 28] TXA may serve as an alternative to using bicarbonate for buffering acidic local anesthetic solutions, with the added effect of hemostasis. Adding TXA to the tumescent mixture may also be beneficial in local anesthesia for liposuction.
While adrenaline was not used during the experimental phase of this study, TXA and adrenaline effect on bleeding control is complementary. Adrenaline reduces bleeding by immediate constriction of blood vessels and TXA stabilizes the clot, thus enhancing hemostasis. Adrenaline is relatively short acting, and some patients tend to bleed after its effect dissipates. The effect of TXA however continues and prevents later onset of bleeding and subcutaneous hematomas. It is possible that a mixture of lidocaine or bupivacaine with adrenaline and TXA will be more effective in controlling bleeding, and this combination

efficacy and safety should be explored in future studies. The literature has identified TXA as a skin lightening agent when used repeatedly,[29-31] however, in our study no cases of hypopigmentation were observed in a follow up examination after 3months.

Since TXA has been shown to inhibit angiogenesis and neovascularization in tumors in an animal model,[32] there was a theoretical risk that TXA could interfere with skin grafts take or flaps survival. We did not observe any difference in outcomes of reconstruction with skin grafts or flaps at the sutures removal after one week, however this should be monitored carefully in similar future studies.

The results of this study may be biased by some factors: location and depth of the surgical wound, the intensity of the cautery used, momentary high peaks of blood pressure while the patient waits between the Mohs stages,(coughing, sneezing, valsalva in the toilet), hormonal factors in women (menstruation, pregnancy). Nevertheless, we have no reason to expect a different distribution of these factors between the relatively large randomized study groups. Future studies should consider potential issues with blinding in the research design. The effect of buffering of the TXA solution on blinding was not considered in this study design, which may provide observable variations in pain during injection between the two groups. It would also be advisable to have more than one surgeon perform the assessments, which would also minimize issues with blinding and provide inter-operator reliability measures. The efficacy of subcutaneous injection of the combined solution described herein can be replicated and evaluated easily by any dermatologic surgeon.

Conclusions

The results of the current study indicate that subcutaneous injection of TXA may reduce

bleeding during and after dermal surgery. The hemostatic- anesthetic mixture proved to be safe and even more effective in patients receiving anticoagulation treatment. The current study supports the increasing tendency among dermatologic surgeons to avoid discontinuation of anti-coagulation drugs prior to surgery. Instead we present a method to minimize the increased bleeding by local enhancement of the coagulation effect. The use of TXA together with the anesthetic agent allows better control of bleeding during and after surgery and potentially less burning sensation during injection. We suggest the use of TXA together with the anesthetic drug routinely in dermatologic surgery.

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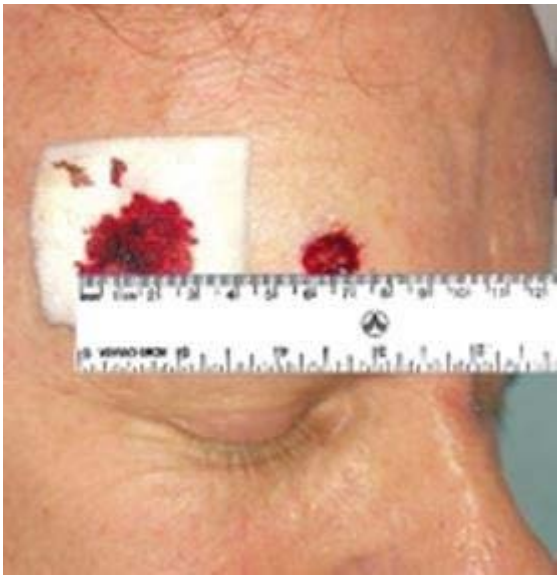

Figure 1. Measurement of sugical woumd amd bloodstain impregnation on a Tefla pad

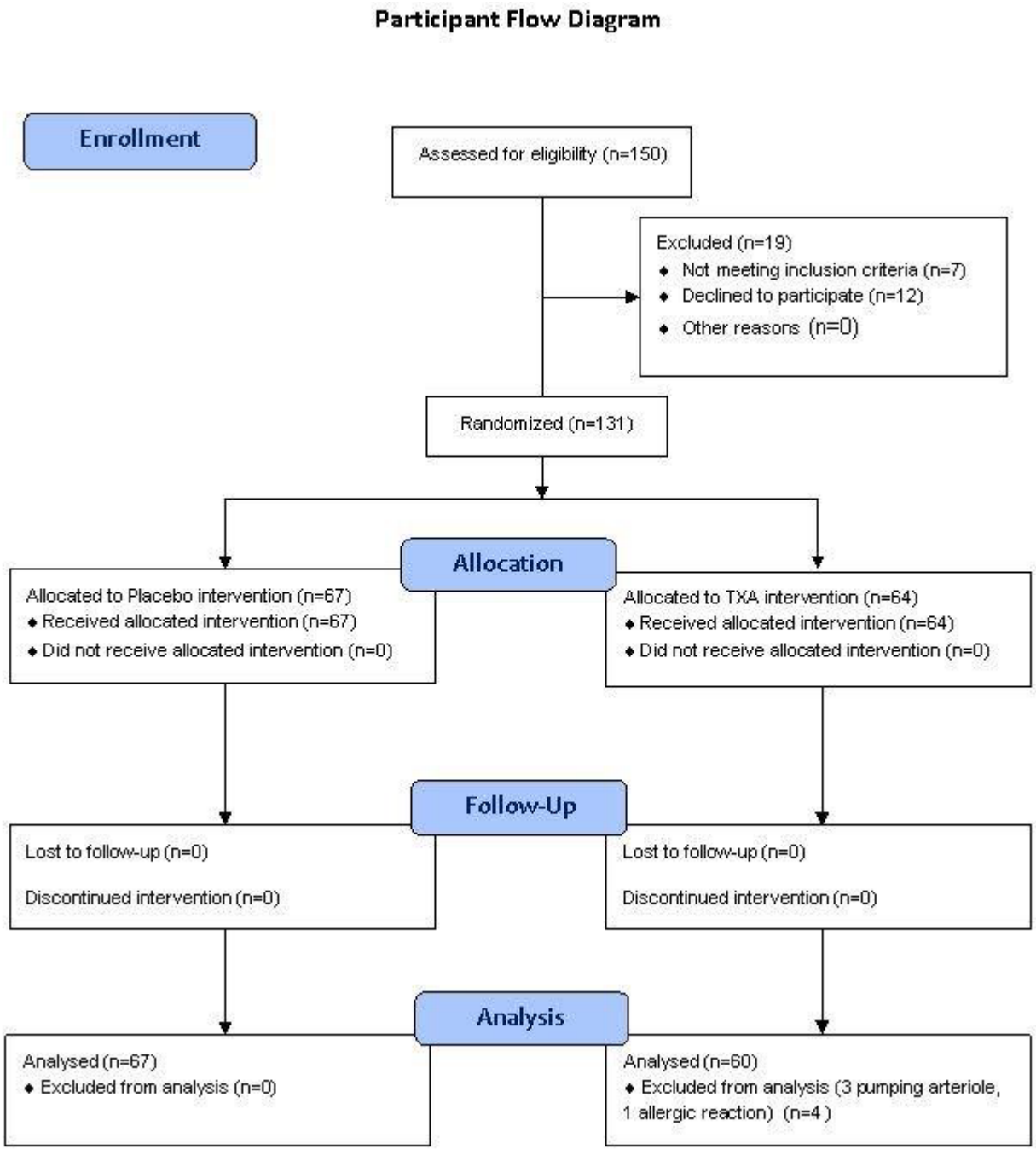

Figure 2. CONSORT flow diagram

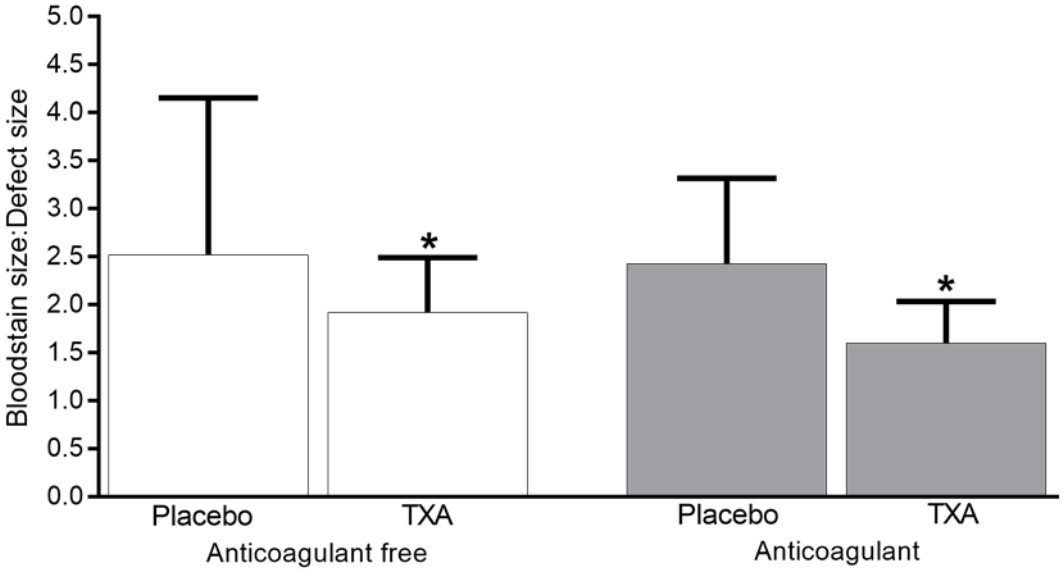

Figure 3. Comparison of blood stain size to surgical wound size ratio between TXA and placebo interventions in the anticoagulant free and anticoagulant subgroups.

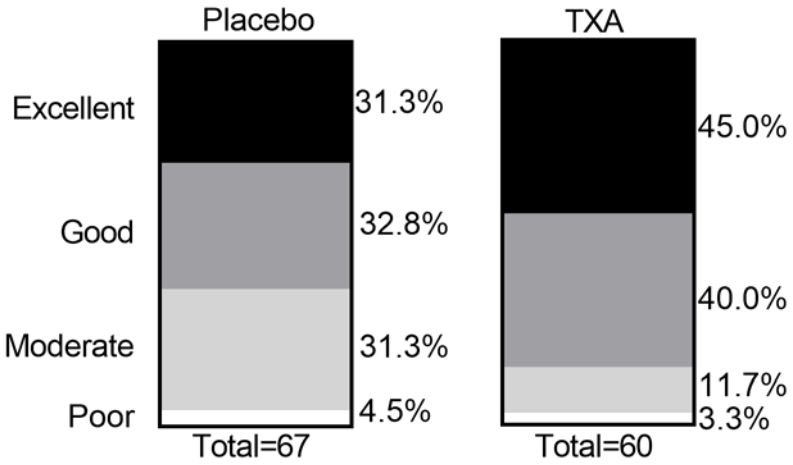

Figure 4. Hemostatic Evaluation by surgeon in the placebo and TXA groups

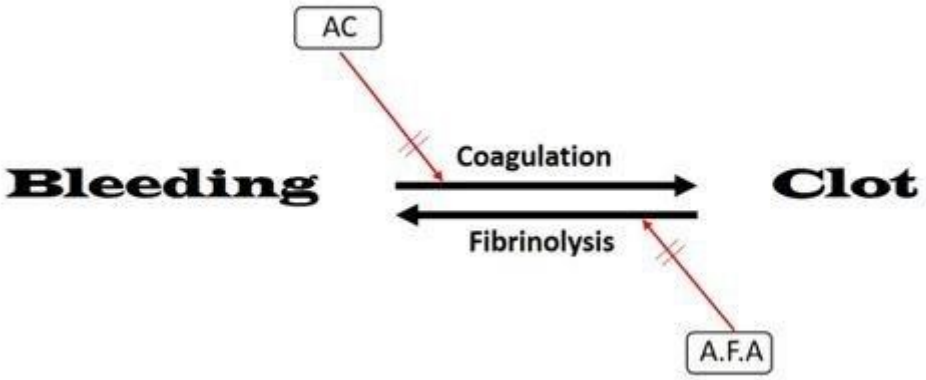

Figure 5. Bleeding to clotting schematic equation

Table 1: Descriptive statistics for placebo and TXA groups

	Placebo	TXA
N (Females)	67 (24)	60 (20)
age [mean (SD)] years	66.2 (14.4)	70.9 (11.4)
BP diastolic [mean (SD)] mmHg	75.8 (8.8)	79.1 (9.3)
BP systolic [mean (SD)] mmHg	141.8 (18.1)	145.5 (20.6)
Smoking	6	4
DVT/PE	3	2
Diabetes	14	14
CVA/TIA	1	1
Hypertension	28	30
Coronary stents	8	10
Dysrhythmia	2	4
CABG	6	5
Anticoagulants	21	28
- Acetyl salicylic acid (Aspirin)	16	22
- Other*	5	6

* coumadin (Warfarin), eliquis (Apixaban), clopidogrel (Plavix), enoxaparin (Clexane) and rivaroxaban (Xarelto).

Table 2: Comparison of wound and bloodstain size in the placebo and TXA groups

	Placebo	TXA	Mean Difference (95% CI)	p
Defect Size (cm)	1.41 (0.78)	1.69 (0.75)	0.28 (0.24, 9.20)	0.043
Bloodstain Size (cm)	2.95 (1.35)	2.77 (0.93)	-0.18 (-0.58, 0.22)	0.387
Bloodstain/Defect	**2.49 (1.44)**	**1.77 (0.53)**	**-0.72 (-1.09, -0.35)**	**<0.001**

Table 3: Hemostatic Evaluation by Surgeon in the Placebo or TXA groups for anticoagulant-free and anticoagulant subgroups, *n* (%).

	Excellent	*Good*	*Moderate*	*Poor*	p
Anticoagulant-free					
Placebo	18 (39.1)	13 (28.3)	14 (30.4)	1 (2.2)	0.340
TXA	10 (31.3)	15 (46.9)	6 (18.8)	1 (3.1)	
Anticoagulant					
Placebo	3 (14.3)	9 (42.9)	7 (33.3)	2 (9.5)	0.001
TXA	17 (60.7)	9 (32.1)	1 (3.6)	1 (3.6)	